Supplementary table 2: Glossary of terms used in the PROGRESS series

(Related terms are given in italics with reasons why they are avoided in the series)

Average prognosis—The future course of endpoint occurrence in people with a health related condition. Often expressed as an average, with a measure of variation, absolute risk (or rate) of one or more specific endpoints. *Baseline risk* tends to be used for the risk observed in the control arm of a trial. *Underlying prognosis* suggests that risk may be estimated independent of context, or that the risk is fixed. *Overall prognosis* is less specific than "average prognosis" (which implies a variation). *Natural history*—There is rarely, if ever, a natural situation because there are usually clinical actions including interventions and self care. Furthermore history is an odd word to use, when the focus of interest is the future.
Biomarker—A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.[1] Any biomarker is a potential prognostic factor; but there are prognostic factors which are not biomarkers.
Candidate factor—A factor with a rationale hypothesised to relate to specific endpoints; may be a candidate before the first study to investigate association with prognosis.
Cohort study—A group of people assessed at one or more time points and then followed up over time for endpoints to occur. The investigator may initiate their study before (prospective cohort study) or after the startpoint and endpoint data have been collected (retrospective cohort study). *Follow up study, prospective study* are less specific.
Clinical cohort—Prognosis research study design involving people with a health condition, identified or recruited in relation to clinical care (primary, secondary, tertiary), in which startpoints, endpoints, and prognostic factors are characterised with clinically used measures (including electronic health records), research measures (e.g. genomic, phenotyping, questionnaires), or both.
Confounder—A factor which is correlated with the endpoint and with the prognostic factor of interest. A confounder, when properly controlled for, can explain away some or all of an apparent association between the prognostic factor of interest and the endpoint. *Adjustment factor* is not necessarily a confounder; may be known only to associate with endpoint.
Discovery approaches—Research to identify prognostic factors "agnostic" to biology or other mechanisms, and "free" from specific hypotheses about relation to endpoints. A specific example of such an approach is the genome-wide association study.
Emerging factor—A factor for which the evidence is not yet sufficiently strong that it is known to be causal or has been shown to be clinically useful. Usually there are concerns about residual confounding. "Emerging" has the advantage of implying an evolution of evidence; but the disadvantage that it has a positive connotation. (The term "submerging factors" might be used for those factors which have been reliably shown not to be causal or useful). *Novel factor* is not used because it is ambiguous (it could refer to the measurement or the research into the measurement) and implies a scientific judgement (novel may be considered an advance).

Electronic health records—Data obtained as a result of usual clinical care and recorded in computerised patient records, healthcare administrative systems, disease or other registries. Such data may include phenotypic characterisation of the startpoint and endpoint and prognostic factors. Electronic health record cohorts differ from clinical cohorts in that patient consent is typically not sought and only measures made and recorded in usual clinical care are available (i.e. there are no researcher added measures).
Routine data—Some electronic health data are not standardised or uniform (i.e. routine) but are none the less useful for prognosis research e.g. primary care health records

Endpoint—A health condition evaluated at a time subsequent to the startpoint, which is considered important to prevent (or, if positive health outcome, to promote). The endpoint for one analysis may be the startpoint for another. Events are the subset of endpoints that occur on a specific date. **Outcome** is used as a synonym.

Established (prognostic) factors—Those factors which are already known to be associated with an endpoint given the startpoint and for which adjustment would be expected when studying another prognostic factor. Note established factors for onset of condition are not necessarily the same as those for condition progression. An accumulation of evidence over multiple studies is usually required for a prognostic factor to become established, although what constitutes sufficient evidence is not well defined.
Standard, accepted, factors implies convention and culture.

Exploratory prognostic study—This study examines multiple preliminary analyses often without a clear prior hypothesis; the focus is on not missing a possible effect rather than avoiding false positives.
Confirmatory study—In observational research it is difficult to define when a hypothesis is confirmed, or refuted (despite the common claim "our findings confirm), see replication.

Factor—Any measurement which could be associated with prognosis, irrespective of whether any prognosis research has been carried out on the factor. Factors include measurements made at the level of individuals (health related conditions, biomarkers, socio-demographic) and at an ecological level (healthcare, physical and social environment). Synonym: **variable**.

Health services research examines how people get access to health care, how much care costs, and what happens to patients as a result of this care. The main goals of health services research are to identify the most effective ways to organize, manage, finance, and deliver high quality care; reduce medical errors; and improve patient safety.

Health technology—Any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes the pharmaceuticals, devices, procedures, and organizational systems used in health care. Some prognostic factors, prognostic models, and predictors of differential treatment response constitute health technologies.

Health technology assessment considers the effectiveness, appropriateness, and cost of technologies. It does this by asking four fundamental questions: Does the technology work, for whom, at what cost, and how does it compare with alternatives?

Incremental prognostic value—Improving a prognostic model by adding a new factor. An independent prognostic factor may or may not add prognostic value.

Individual participant data (IPD) meta analysis—Pooling multiple datasets (contrasted with literature based meta-analysis in which only those summary figures are available for analysis). Meta-analysis is the process of statistical analysis of multiple studies in order to obtain quantitative summaries across studies with greater precision and potentially less bias than that obtained within individual studies.
Knowledge management gets the right knowledge to the right people at the right time so they can work more effectively.
Knowledge synthesis—Systematic review of what we know, and what we do not know and how we know it.[2] Includes animal studies, basic science, observational and experimental human studies.
Outcomes research focuses on describing and understanding the relations between startpoint and endpoint in their current clinical and demographic context, and includes health services research relating outcomes to the quality of healthcare.
Personalised medicine approach to tailoring intervention to the specific characteristics of patients.
Phenotype—Any factor, or combination of factors, with both genetic and environmental influences.
Predictor of differential treatment response is one or more factors measured in a person with a given startpoint (e.g. disease or other health condition) which shows a reliable association with differential responses (more benefit or less harm measured on the relative risk scale) to a specific therapy. The term differential refers to a comparison between one treatment compared to another or no treatment, or to different effective doses of the same treatment (e.g pharmacogenetic studies). *Predictive factor* is the term commonly used in cancer but seldom in other clinical areas. Synonyms: *treatment covariate interactions, effect modifier, effect interaction, effect moderator*.
Predictors of differential treatment response—Research questions focus on the identification, validation and assessment of impact of predictors of differential treatment response in order to identify groups of people with a condition who will have greater benefit or less harm from a specific therapeutic strategy. Such predictor are one or more factors measured in a person with a given startpoint (e.g. disease or other health condition) which show a reliable association with differential responses (more benefit or less harm) to a specific therapy. The term differential refers to a comparison between one treatment compared to another or no treatment, or to different effective doses of the same treatment (e.g pharmacogenetic studies).
Prognostic factor—Any measurement which, among people with a given startpoint, is associated in one or more studies with (higher or lower) risk of a subsequent endpoint. Related terms: **Independent factor**—An effect (e.g. relative risk) of a prognostic factor of interest is observed after controlling for established prognostic factors, confounders or both. **Risk stratifier**—A single prognostic factor useful in clinical decision making. *Risk factor, risk exposure* tend to be used in healthy populations rather than those with a startpoint. Predictor prognostic factors may not add useful prediction to prognostic models. *Prognostic determinant* should be reserved for those prognostic factors with a proven role in causation.

Prognostic factor research questions focus on discovering and evaluating factors which may be useful as modifiable targets for interventions to improve prognosis, building blocks of prognostic models, or predictors of differential treatment response.
Prognostic marker denotes the subset of prognostic factors which indirectly measure the variable of interest. For example, CEA is a prognostic marker of the extent of metastases; HbA_{1C} is a prognostic marker of the glucose in the last 120 days. *Surrogate marker* suggests that the substitution is for the marker.
Prognostic model is a numeric representation (i.e. model) estimating the likelihood of a specific endpoint given a person's values for a set of prognostic factors. Many combinations of terms are used in the literature: *clinical* + (*prognostic*, *risk*, *prediction*) + (*model*, *rule*, *score*, *index*, *stratifier*). We avoid these because, for example, risk prediction model is less widely used that prognostic model , it may imply use in healthy populations and it is tautologous (what else could be predicted if not risk?). The term *rule* implies deterministic (rather than supportive) relation with clinical actions.
Prognostic model research questions focus on the development, validation and assessment of clinical impact of models in order to identify groups of people with different endpoint risk. Prognostic models have a range of uses including guiding therapeutic decisions, and adjusting for case mix.
Prognosis research inquires into the occurrence of future health conditions (endpoints) among people with a given health condition (startpoint) in order to inform decision making at different points along pathways to improving health. Most, but not all, prognosis research is applied research. A generic term spanning research into outcomes, prognostic factors, prognostic models and predictors of differential treatment response.
Registry (disease, drug, procedure) is an system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.[3] *Register* a list of people or studies in the registry; the registry is the whole dataset held for people or other entity in the register.
Replication—Repeating a study, often under slightly different circumstances, to test whether findings are consistent. **Validation** is a widely used related term.
Reporting guidelines—Statements that provide advice on how to report research methods and findings. Usually in the form of a checklist, flow diagram or explicit text, they specify a minimum set of items required for a clear and transparent account of what was done and what was found in a research study, reflecting in particular issues that might introduce bias into the research.[4]
Startpoint—A health condition characterised in sufficient (context dependent) detail for clinical action at a certain date. A health condition is usually associated with self perceived ill health or actions by a health professional. Health conditions are broader in scope than diagnosed disease and include syndromes, test results and interventions, physiological conditions, symptoms, functional impairment and quality of life, health behaviours and psychosocial factors. The date (or time) from which follow-up is measured ("time zero') is clear for some conditions (e.g. first hospitalisation for acute myocardial infarction) but harder to define for "longitudinal phenotypes" such as chronic, episodic, insidious onset conditions (e.g. angina, low back pain).

Statistical analytic protocol—A plan setting out sufficient details of the planned statistical analysis so that a third party could , at least in principle, (i) see which analyses were specified at which stage of the research process (in particular which were specified prior to receiving a dataset) and (ii) (in some cases) replicate the analyses. The analytical protocol history provides the rationale for any changes to the first version. It may be part of the study protocol or, commonly, a separate document written at a different time and by different people from those who wrote the study protocol. *Secondary analysis* is analysis of data planned after its collection; it may or may not be related to the original purpose for which the data were collected.[5] This is a common situation in prognosis research. We avoid the term secondary analysis because clear distinction with primary analysis is difficult; what is more important is transparency in registering studies, and publicly available study and statistical analytic protocols.

Stratified medicine—The tailoring of therapeutic decisions to specific, often biologically distinct, groups of individuals, based on tests which predict differential (on the relative risk scale) endpoint response to a specific treatment.

Study protocol describes the objective(s), design, methodology, and measurements, statistical considerations, and organization of a study,[6] usually written before the conduct of the study.

Study registration—Submission of standard details of a study to a publicly accessible registry

Translational research transforms scientific discoveries and new approaches arising from laboratory, clinical, or population studies into clinical and policy applications to reduce the incidence of fatal and non-fatal endpoints. Prognostic factors, prognostic models and predictors of differential treatment response represent new approaches which can be used to improve health. New approaches which are not adequately developed and evaluated or, once shown to be worthwhile, are not implemented in clinical practice have been described as failing in the **first and second gaps in translation** respectively.

Transparency measures—A range of activities concerned with the openness of research (including study registration, publicly accessible study protocols, clear study reporting and data sharing) which may contribute to improvements in research quality.

Validation—Repeating a study, often under slightly different circumstances and in different study populations, to test whether findings are consistent and accurate. Validation studies provide estimates of a model's ability to discriminate between patients with different outcomes and of the agreement between predicted and observed risks

1 Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Therapeutics* 2001;(69):89-95.

2 Khoury MJ, Gwinn M, Ioannidis JP. The emergence of translational epidemiology: from scientific discovery to population health impact. *Am J Epidemiol* 2010;172:517-24.

3 Agency for Healthcare Research and Quality. Effective Health Care Program. Registries for evaluating patient outcomes: a user's guide (executive summary May 16 2007).

www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=12.

4 EQUATOR Network. www.equator-network.org (updated 2009).

5 Stewart D, Kamins M. *Secondary research: information sources and methods*. 2nd ed. Sage Publications, 1993.

6 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised tripartite guideline. Guideline for good clinical practice. E6(R1)*. 1996. www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html.